Synthesis of 3-(2',3',4'-Trimethoxyphenyl)isocoumarin and its Dihydro- derivative

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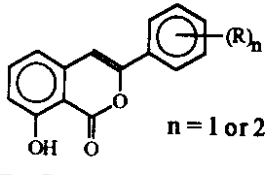
Summary: 3-(2',3',4'-Trimethoxyphenyl)isocoumarin (**7**) was synthesized by the condensation of homophthalic acid (**5**) with 2,3,4-trimethoxybenzoyl chloride (**6**) which on alkaline hydrolysis gave the keto-acid (**8**). (dl)-3-(2',3',4'-Trimethoxyphenyl)-3,4-dihydroisocoumarin (**11**) was obtained by reduction of the keto-acid (**8**) to racemic hydroxy-acid (**10**) followed by cyclodehydration using acetic anhydride.

Introduction

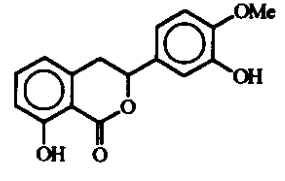
Various 3-phenylisocoumarins with methoxy substituents at 3-phenyl group have been found in literature showing different activities. 3-(4'-Methoxyphenyl)isocoumarin was found to have antifungal activity [1]. 3-Phenyl derivatives of isocoumarins (**1**) are used in sunscreen creams to absorb UV light [2]. Some other derivatives of 3-(methoxyphenyl)isocoumarin have also been reported to have significant importance like phyllodulcin (**2**) which is 400 times sweeter [3] than sucrose. It is a sweetener ingredient of health drinks [4] and has no toxic effects [5]. The same compound and its derivative (**3**) are also used as tobacco flavourant [6]. Phyllodulcin exhibit antioxidant property for oils and fats [7]. Another derivative of methoxyphenylisocoumarin (agrimonolide, **4**) is reported to have anthelmintic activity [8]. Thunberginol C, D, E and G show antiallergic and



n = 1 or 2

R= C_{1-4} alkyl, C_{1-4} alkoxyl, methylidioxy, phenoxy

(1)



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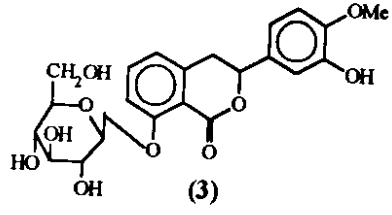

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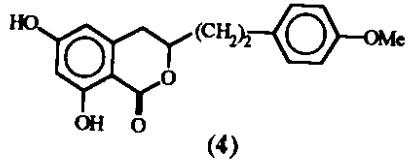

(4)

antimicrobial activities [9]. Thunberginol A, B and F have been observed more potent antiallergic than phyllodulcin. They exhibit antimicrobial activity against oral bacteria [10].

In view of above findings and as a continuation of our previous studies [11,12] we

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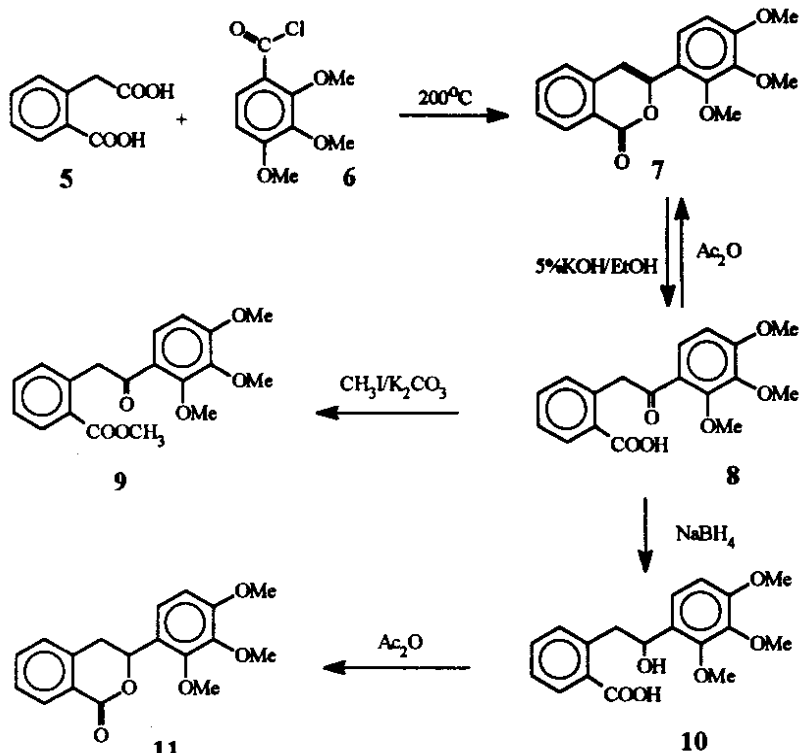
report here the syntheses of new 3-(2',3',4'-trimethoxyphenyl)isocoumarin (7) and (dl)-3-(2',3',4'-trimethoxyphenyl)-3,4-dihydroisocoumarin (11). Condensation of 2',3',4'-trimethoxybenzoyl chloride (6) with homophthalic acid (5) at 200°C afforded 3-(2',3',4'-trimethoxyphenyl)isocoumarin (7). This isocoumarin (7) showed characteristic 1H singlet at δ 7.28 for C_4-H and lactonic absorption in IR spectrum at 1720 cm^{-1}. The mass spectrum of this compound showed molecular ion peak at m/z 312 (base peak) which agrees with its molecular weight. HREIMS of this ion is in good agreement with the calculated value. Alkaline hydrolysis of (7) yielded the keto-acid (8) which showed 2H singlet at δ 4.69 for benzylic $-CH_2$ in ^{1}H-NMR while ketonic and carboxylic carbonyl absorption in IR was observed at 1720-1680 cm^{-1}. The mass spectrum of this keto-acid (8) showed characteristic peak at m/z 312 [M^+-H_2O] and HREIMS of the molecular ion of this compound is in good agreement with the calculated value. Isocoumarin (7) was obtained back on refluxing the keto-acid (8) with acetic anhydride. Methylation of (8) with excess of methyl iodide yielded the methyl keto-ester (9). This ester (9) was confirmed by 3H singlet for $COOCH_3$ at δ 4.03 in ^{1}H-NMR while ketonic and ester carbonyl absorption in IR spectrum appeared at 1710-1680 cm^{-1}. The mass spectrum of this keto-ester (9) showed characteristic peak at m/z 312 [M^+-CH_3OH] and HREIMS of its molecular ion is in good agreement with the calculated value. Sodium borohydride reduction of keto-acid (8) furnished corresponding racemic hydroxy-acid (10) which was refluxed with acetic anhydride in crude form to produce (dl)-3-(2',3',4'-trimethoxyphenyl)-3,4-dihydroisocoumarin (11). This dihydroisocoumarin (11) showed the typical AB pattern for C_3-H and typical ABX pattern for C_4-H protons in ^{1}H-NMR spectrum. Thus each proton of C_4-H showed doublet of doublet at δ 3.04-3.35. The doublet of doublet for C_3-H was observed at δ 5.70. This dihydroisocoumarin (11) showed carbonyl absorption at 1720 cm^{-1} in IR spectrum. In mass spectrum, the molecular ion peak was observed at m/z 314 along with the base peak at m/z 118 and HREIMS of the molecular ion was in good agreement with the calculated value as shown in Table-II which further confirmed the structures of this compound. These compounds (7-11) have been prepared for the investigation of kinetic studies. Antimicrobial activity of these compounds will be published separately.



Synthetic Scheme

Experimental

Melting points of the compounds were determined in open capillaries using Gallenkemp melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded on a Hitachi model 270-50 spectrophotometer as KBr discs or as neat liquids. ^{1}H-NMR (500MHz) spectra were recorded on a Bruker AM-500 as $CDCl_3$ solutions using TMS as internal standard and EIMS were recorded on a MAT-112-S machine.

3-(2',3',4'-Trimethoxyphenyl)isocoumarin (7)

A mixture of homophthalic acid (5) (11.0 mmol) and 2,3,4-trimethoxybenzoyl chloride (6) (46 mmol) was heated under reflux at 200°C for 4 hr. The residue after concentration was chromatographed on silica gel column using pet. ether (60-80°) and recrystallized from methanol to give the isocoumarin (7) (6.6 mmol, 60%, mp 91-92°C). IR (ν_{max}, KBr, cm^{-1}): 1720, 1635; ^{1}H-NMR ($CDCl_3$ δ-values): 3.91, (6H, s, 2xOCH_3), 3.93 (3H, s, 2'-OCH_3), 6.76 (1H, d, J=9.0 Hz, H-5'), 7.28 (1H, s, H-4), 7.44-7.48 (2H, m, H-7,5), 7.62 (1H, d, J=9.0 Hz, H-6'), 7.69 (1H, ddd, J=7.6, 1.4 Hz, H-6), 8.28 (1H, dd, J=8.3, 1.5 Hz, H-8); EIMS (70ev): m/z (%) = 312 (100) [M$^+$], 284 (51.8) 269 (42.3), 183 (48.2). HREIMS $C_{18}H_{16}O_5$: calcd. 312.0998, found 312.0996.

2-(2',3',4'-Trimethoxybenzoylmethyl)benzoic acid (8)

A solution of 3-(2',3',4'-trimethoxyphenyl) isocoumarin (7) (2.0 mmol) in ethanol (20 mL) and potassium hydroxide (5%, 30 mL) was refluxed for 4hr. Ethanol was removed from the reaction mixture under reduced pressure. Cold water (20 mL) was added and the reaction mixture was acidified with hydrochloric acid and then extracted with ethyl acetate (2x25mL), dried (Na_2SO_4) and solvent rotary evaporated to yield a crude solid which was recrystallized from ethyl acetate to give (8) (1.6 mmol, 80%, mp 138°C). IR (ν_{max}, KBr, cm^{-1}): 1710, 1680. ^{1}H-NMR ($CDCl_3$, δ-values): 3.89 (3H, s, 4'-OCH_3), 3.91 (3H, s, 3'-OCH_3), 4.00 (3H, s, 2'-OCH_3), 4.69 (2H, s, CH_2), 6.72 (1H, d, J=8.9 Hz, H-5'), 7.25 (1H, dd, J=4.3, 3.3 Hz, H-3), 7.36 (1H, dd, J=7.6 Hz, H-5), 7.50 (1H, d, J=8.9 Hz, H-6'), 7.52 (1H, dd, J=3.3 Hz, H-4), 8.07 (1H, d, J=7.8 Hz, H-6), 10.34 (1H, bs COOH, D_2O exchangeable); EIMS (70ev): m/z (%) = 330(3.3) [M$^+$], 312(28.1) [M$^+$-H_2O], 195(100), 152(40.3). HREIMS $C_{18}H_{18}O_6$: calcd. 330.1103, found 330.1110.

The keto-acid (8) was converted back into isocoumarin (7) on refluxing with acetic anhydride for 1 hr. This isocoumarin also has the same R_f value as of that synthesized earlier.

Methyl 2-(2',3',4'-trimethoxybenzoylmethyl)bnzoate (9)

The keto-acid (8) (0.39 mmol), methyl iodide in excess and anhydrous potassium carbonate (1.5 g) in dry acetone (15 mL) were heated under reflux for 2 hr. The reaction mixture was filtered while hot. The cake was washed with warm dry acetone (10 mL) and solvent evaporated to leave an oil which was purified by column chromatography using silica gel and pet. Ether to afford methyl 2-(2',3',4'-trimethoxybenzoylmethyl)benzoate (9) (.33 mmol, 85%, oil). IR (ν_{max}, neat, cm^{-1}): 1710, 1690. ^{1}H-NMR ($CDCl_3$, δ-values): 3.76 (3H, s, 4'-OCH_3), 3.89 (3H, s, 3'-OCH_3), 3.91 (3H, s, 2'-OCH_3), 4.03 (3H, s, $COOCH_3$), 4.68 (2H, s, CH_2), 6.73 (1H, d, J=8.9 Hz, H-5'), 7.24 (1H, dd, J=0.9, 7.8 Hz, H-3), 7.35 (1H, ddd, J=7.7, 1.3 Hz, H-5), 7.48 (1H, ddd, J=7.5, 1.5 Hz, H-4), 7.57 (1H, d, J=8.9 Hz, H-6'), 8.02 (1H, dd, J=7.8, 1.4 Hz, H-6); EIMS (70ev): m/z (%) = 344(6.21) [M$^+$], 312(10.96) [M$^+$-CH_3OH], 195(100), 149(36.91). HREIMS $C_{18}H_{20}O_6$: calcd. 344.1260, found 344.1265.

(dl)-3-(2',3',4'-Trimethoxyphenyl)-3,4-dihydroisocoumarin (11)

A solution of the keto-acid (8) (0.5g, 1mmol) in 1% potassium hydroxide solution (25mL) and sodium borohydride (0.20g) was stirred overnight at room temperature. After being acidified with HCl, the whole mixture was extracted with dichloromethane (2x15 mL). Usual work-up gave crude racemic hydroxy-acid (10) (0.40g). This compound (10) was dissolved in acetic anhydride (1mL) and heated under reflux for 2 hr. The mixture was cooled, water (15mL) was added and the whole was stirred continuously overnight and extracted with CH_2Cl_2 (2x20 mL). The solvent was removed by vacuum distillation. The crude compound was purified by column chromatography on silica gel with pet. ether and recrystallized from methanol to

furnish (dl)- 3-(2',3',4'-Trimethoxyphenyl)-3,4-dihydroisocoumarin (11) (0.8 mmol, 80%, mp 114°C). IR (ν_{max}, KBr, cm^{-1}): 1720, 1615. ^{1}H-NMR ($CDCl_3$ δ-values): 3.07 (1H, dd, J=16.3, 3.1 Hz, H-4a), 3.30 (1H, dd, J=16.3, 12.2 Hz, H-4b), 3.88, (6H, s, 2xOCH_3), 3.92 (3H, s, OCH_3), 5.77 (1H, dd, J=12.2, 3.1 Hz, H-3), 6.72 (1H, d, J=8.7 Hz, H-5'), 7.24 (1H, d, J=8.6 Hz, H-6'), 7.27 (1H, d, J=7.5 Hz, H-5), 7.42 (1H, dd, J=7.6 Hz, H-7), 7.55 (1H, ddd, J=7.5, 1.26 Hz, H-6), 8.14 (1H, d, J=7.6 Hz, H-8); EIMS (70ev): m/z (%) = 314 (33.3) [M^+], 239 (3.6) 118 (100). HREIMS $C_{18}H_{18}O_5$: calcd. 314.1154, found 314.1150.

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